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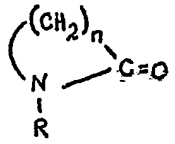
(54) NEW N-SUBSTITUTED LACTAMS

(71) We, UCB, a Société Anonyme (formerly known as UCB (Union Chimique-Chemische Bedrijven) Société Anonyme), of 4, Chaussée de Charleroi, Saint-Gilles-lez-Bruxelles, Belgium, a Body Corporate organised under the laws of Belgium, do hereby declare the invention, for which we pray that patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

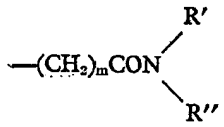
The present invention is concerned with new N-substituted lactams and with the preparation thereof, as well as with their use for therapeutic purposes.

The present invention is an addition to our British Patent Specification No. 1,039,113.

In our British Patent Specification No. 1,039,113, there are described and claimed N-substituted lactams of the general formula:—



wherein n is 3, 4 or 5, R is a radical of the formula:



in which m is 0, 1 or 2, R′ is a hydrogen atom or an alkyl, cycloalkyl, alkenyl, alkynyl aryl radical and R″ is a hydrogen atom or an alkyl radical or R′ and R″, together with the nitrogen atom to which they are attached, form a heterocyclic ring.

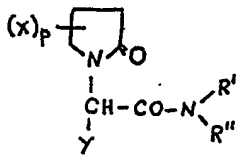
These compounds can be used for therapeutic purposes, for example, for the treatment of motion sickness, hyperkinesia, hypertonia and epilepsy. They are active in the central nystagmus test (see J. Lachmann et al., Amer. J. Physiol. *193*, 328—334/1958) which is an indication of the activity of these compounds against motion sickness (see W. J. Oosterveld, "Effects on Central Nystagmus", Thesis, Amsterdam, Drukkerij Van Wijk/Oostzaan, 1963, p. 59).

Furthermore, subsequent pharmacological studies have shown that the activity of these compounds on the central nervous system is considerably greater than was initially expected. For example, these compounds appear to have a beneficial activity

in the treatment of vertigo, especially of central origin, and also of mnesic phenomena in normal and pathological conditions (see C. E. Giurgea, F. E. Moeyersoons and A. G. Evraerd, Arch. int. Pharmacod., *166*, 238/1967; F. E. Moyersoons, A. Evraerd J. Dauby and C. E. Giurgea, loc. cit., *179*, 388/1969; F. Mouravieff-Lesuisse and C. E. Giurgea, loc. cit., *176*, 471/1968).

In continuation of the work in this field, we have now found compounds similar to general formula as given above but in which n is 3 and m is 1 and in which at least one of the hydrogen atoms in the cyclic methylene groups and/or in the methylene group in the side chain is replaced by a substituent of the kind defined hereinbelow, also have the same pharmacological activities as the compounds disclosed in our British Patent Specification No. 1,039,113.

According to the present invention, there are provided new N-substituted lactams of the general formula:—



(I)

wherein X is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, p is a whole number of from 1 to 6, Y is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms or a cycloalkyl radical and R′ and R″, which may be the same or different, are hydrogen atoms or alkyl, alkenyl, alkynyl, cycloalkyl or aryl radicals or R′ and R″, together with the nitrogen atom to which they are attached, form a heterocyclic radical which may contain further heteroatoms, with the proviso that at least one of the symbols X and Y is other than a hydrogen atom.

In the central nystagmus test mentioned above, it was found that the intravenously administered active dose in rabbit is 3 mg/kg body weight for (5,5-dimethyl-2-oxo-pyrrolidino)-acetamide and between 10 and 20 mg/kg body weight for the following other compounds according to the present invention:

2-(2-oxo-pyrrolidino)-propionamide
(5-methyl-2-oxo-pyrrolidino)-acetamide
(4-methyl-2-oxo-pyrrolidino)-acetamide
(3,5-dimethyl-2-oxo-pyrrolidino)-acetamide
2-(5-methyl-2-oxo-pyrrolidino)-butyramide
(4,5-dimethyl-2-oxo-pyrrolidino)-N,N-dimethylacetamide

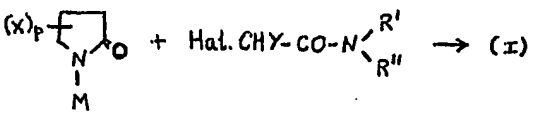
On the other hand, the compounds of the present invention prove to possess a mnesic activity as demonstrated by the spinal fixation test (cf. T. J. Chamberlain, P. Halik and R. W. Gerard, J. Neuro-physiol. *26*, 662/1964). A shortening of the time for spinal fixation is an indication that the compounds might be useful in the field of memory troubles. This shortening of spinal fixation time is observed at the following doses (in mg/kg body weight) when intraperitoneally administered into rats:

(3,5,5-trimethyl-2-oxo-pyrrolidino)-acetamide	:	55
(4-methyl-2-oxo-pyrrolidino)-acetamide	:	156
2-(2-oxo-pyrrolidino)-propionamide	:	200

Moreover, the compounds of the present invention bring about a decrease in cerebral excitability, as demonstrated by the audiogenic seizure test in mice (E. A. Swinyard, "Some physiological properties of audiogenic seizure in mice and their alteration by drugs", in "Psychophysiologie, neuropharmacologie et biochemie de la crise audiogene", p. 405—421, Edition Centre Nat. Rech. Scient., Paris, 1963). The compounds of the present invention are active in the tonic phase of the audiogenic seizure at an intraperitoneally administered dose of about 200 mg/kg body weight.

The new compounds according to the present invention can be prepared, for example, by one of the following methods:

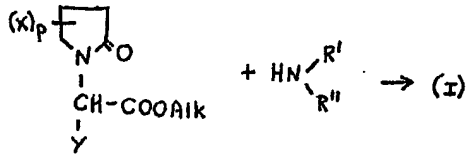
1) reaction of a metallic derivative of an $(X)_p$-substituted 2-pyrrolidinone (II) with a 2-halo-2-Y-N-R'-N-R''-acetamide (III) according to the equation:—



(II) (III)

in which R', R'', X, Y, n and p have the same meanings as given above, M is an alkali metal atom and Hal is a halogen atom; or

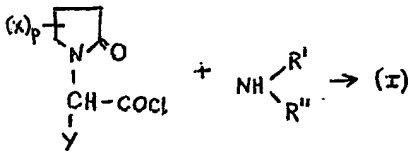
2) reaction of an alkyl 2-[$(X)_p$-pyrrolidino]-2-Y-acetate (IV) with a nitrogen compound R'—NH—R'' (V) according to the equation:—



(IV) (V)

in which Y, R', R'', X, n and p have the same meanings as given above and Alk is a lower alkyl radical; or

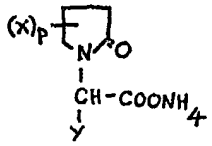
3) reaction of a 2-[$(X)_p$-pyrrolidino]-2-Y-acetyl halide (VI) with a nitrogen compound R'—NH—R'' (V) according to the equation:—



(VI) (V)

in which Y, R', R'', X, n and p have the same meanings as given above.

In the particular case of compounds of general formula (I) in which R' and R'' both represent hydrogen atoms, they can also be prepared by the thermal dehydration of an ammonium 2-[$(X)_p$-2-oxo-pyrrolidino]-2-Y-acetate of the general formula:—



(VII)

in which X, Y, n and p have the same meanings as given above.

The new compounds of general formula (I) can be administered per os, parenterally (particularly by intravenous injection) or rectally.

According to the present invention, the compositions to be used for the treatment of motion sickness, hyperkinesia, hypertonia, epilepsy and mnesic troubles contain, as active constituent, an N-substituted lactam of general formula (I) and solid or liquid pharmaceutical excipients commonly used for the preparation of formulations suitable for oral, parenteral and rectal administration.

The compositions of the invention to be used for oral administration may be solid or liquid, for example in the form of tablets, pills, gelatine capsules, solutions, syrups and the like. In like manner, the compositions to be used for parenteral

administration are the known pharmaceutical forms for this kind of administration, such as aqueous or oily solutions, suspensions or emulsions. Compositions for rectal administration are generally in the form of suppositories.

The pharmaceutical forms, such as injectable solutions, injectable suspensions, tablets, drops, suppositories and the like, are prepared by the common methods known to pharmacists.

The active lactams of the present invention are mixed with a non-toxic pharmaceutically acceptable solid or liquid excipient and possibly with a dispersing or stabilising agent. Preservatives, sweetening agents and colouring agents may, if desired, also be added.

Solid or liquid pharmaceutical vehicles are also well known in the art. Solid pharmaceutical excipients for the preparation of tablets and capsules include, for example, starch, talc, calcium carbonate, lactose, sucrose and magnesium stearate.

The percentage of active material in the pharmaceutical compositions may vary within wide limits according to the conditions of use and, in particular, according to frequency of administration.

The suitable posology varies between 100 and 2000 mg. of active product per day.

The compositions of the present invention may, for example, be administered *per os* at a dosage of 1 to 4 tablets or capsules per day containing 100, 200, 400 or 500 mg. of active product or by repeated intravenous injections of 1 or 2 ml. aqueous solutions containing 10% active material.

The following composition is given by way of example, of a composition according to the present invention to be administered *per os* in tablet form:

(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide	:	400 mg.
starch	:	61 mg.
polyvinylpyrrolidone	:	8 mg.
talc	:	26 mg.
magnesium stearate	:	5 mg.

For the preparation of 10% aqueous solutions suitable for parenteral administration, the following procedure may be followed:

10 g. of (5,5-dimethyl-2-oxo-pyrrolidino)-acetamide are dissolved in distilled water and the volume is adjusted to 100 ml. The solution is filtered and 2 ml. phials are filled with this solution and are then sterilised in known manner.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1

(5-methyl-2-oxo-pyrrolidino)-N,N-diethyl-acetamide

An ethanolic solution containing 10.2 g. (0.15 mole) sodium ethylate is added to a solution of 14.85 g. (0.15 mole) 5-methyl-pyrrolidinone in 300 ml. toluene. The ethanol is progressively distilled off and replaced by toluene until the temperature of the vapours reaches 110°C.

The reaction mixture is then cooled to about 70°C. and 25 g. (0.15 mole) N,N-diethyl-chloroacetamide are added thereto and the same temperature is maintained for 4 hours.

After the reaction mixture has cooled to ambient temperature, it is filtered over "Hyflocel". The filtrate is concentrated and the residue is then distilled under reduced pressure.

There is obtained (5-methyl-2-oxo-pyrrolidino)-N,N-diethyl-acetamide in a yield of 80% of theory; b.p. 128°/0.01 mm.Hg.

The sodium derivative of 5-methyl-2-pyrrolidinone may also be obtained by the action of sodium hydride or sodamide in an appropriate solvent.

Example 2

(3-methyl-2-oxo-pyrrolidino)-acetamide

A solution of 55.5 g. (0.3 mole) ethyl (3-methyl-2-oxo-pyrrolidino)-acetate in 300 ml. methanol is saturated with gaseous ammonia at 20°C. After leaving to stand overnight, the reaction mixture is just evaporated to dryness. The residue is dissolved in 50 ml. ethanol and then 70 ml. anhydrous ether are added. (3-methyl-2-oxo-pyrrolidino)-acetamide separates in the form of crystals which melt at 114°. The yield is 50% of theory.

The same synthesis can also be carried out in an autoclave by heating the reaction mixture at about 100°C. for several hours. The reaction mixture is evaporated to dryness and the residue is recrystallised from an appropriate solvent. By this process, there is prepared, starting from ethyl 2-(2-oxo-pyrrolidino)-propionate, 2-(2-oxo-pyrrolidino)-propionamide in a yield of 80% of theory; after recrystallisation from isopropanol, the compound has a melting point of 125°. It is the same as the compound mentioned in Example 5.

The esters used as starting materials in this process are obtained by preparing the sodium derivative of the appropriate pyrrolidin-2-one, for example, by reaction with sodium methylate or sodium hydride, whereafter this sodium derivative is reacted with an appropriate alkyl haloalkylcarboxylate. In this manner, there are prepared the following esters, which are also new compounds:

ethyl 4-methyl-2-oxo-pyrrolidino-acetate; b.p. 90—96°C./0.05 mm.Hg.;
ethyl (5-methyl-2-oxo-pyrrolidino)-acetate; b.p. 140—145°C./12 mm.Hg.;
ethyl (3,5-dimethyl-2-oxo-pyrrolidino)-acetate (cis-trans mixture); b.p. 100—105°C./0.05 mm.Hg.;
ethyl (4,5-dimethyl-2-oxo-pyrrolidino)-acetate (cis-trans mixture); b.p. 120—125°C./0.05 mm.Hg.;
ethyl (3,3-dimethyl-2-oxo-pyrrolidino)-acetate; b.p. 85°C./0.03 mm.Hg.;
ethyl (5,5-dimethyl-2-oxo-pyrrolidino)-acetate; b.p. 112—115°C./0.1 mm.Hg.;
ethyl (3,5,5-trimethyl-2-oxo-pyrrolidino)-acetate; b.p. 120—125°C./0.1 mm.Hg.;
ethyl (5-ethyl-2-oxo-pyrrolidino)-acetate; b.p. 95°C./0.4 mm.Hg.;
methyl 2-(2-oxo-pyrrolidino)-butyrate; b.p. 80°C./0.01 mm.Hg.; (using methyl 2-bromobutyrate);
ethyl 2-(2-oxo-pyrrolidino)-3-methyl-butyrate; b.p. 148°C./13 mm.Hg.; (using ethyl 3-methyl-2-bromobutyrate);
ethyl 2-(5-methyl-2-oxo-pyrrolidino)-propionate; b.p. 110—115°C./2 mm.Hg.;
ethyl 2-(5-methyl-2-oxo-pyrrolidino)-butyrate; b.p. 118—120°C./2 mm.Hg.;
ethyl 2-(4-methyl-2-oxo-pyrrolidino)-propionate; b.p. 162—166°C./1 mm.Hg.;
ethyl 2-(4-methyl-2-oxo-pyrrolidino)-butyrate; b.p. 93—95°C./0.05 mm.Hg.;
ethyl (4,5-dimethyl-2-oxo-pyrrolidino)-acetate (cis-trans mixture); b.p. 102—105°C./1.5 mm.Hg.;
ethyl (3,4-dimethyl-2-oxo-pyrrolidino)-acetate; b.p. 110°C./0.1 mm.Hg.;
ethyl (4,4-dimethyl-2-oxo-pyrrolidino)-acetate; b.p. 90°C./0.01 mm.Hg.;
ethyl 2-(2-oxo-5,5-dimethyl-pyrrolidino)-butyrate; b.p. 130°C./2 mm.Hg.;

Example 3

2-(5-methyl-2-oxo-pyrrolidino)-butyramide

18.5 g. (0.1 mole) 2-(5-methyl-2-oxo-pyrrolidino)-butyric acid (m.p. 106—107°C.), suspended in 100 ml. anhydrous ether, are treated with 8 g. anhydrous pyridine; thereafter, at a temperature below 0°C., there is added a solution of 12 g. thionyl chloride in 100 ml. anhydrous benzene. The reaction mixture is stirred for 3 hours at ambient temperature. Thereafter, the pyridine hydrochloride which separates is removed by decantation.

The solution of acid chloride formed is evaporated under reduced pressure at a temperature of 30—35°C., the residue is taken up in acetone and then there is added an excess of gaseous ammonia dissolved in methanol.

After stirring for several hours at ambient temperature, the reaction mixture is evaporated to dryness and the residue is taken up in 100 ml. isopropanol. After filtering off the ammonium chloride formed, the filtrate is evaporated to dryness. The residue obtained in this manner is recrystallised from a mixture of ethanol and hexane; there is obtained, in a yield of 60% of theory, 2-(5-methyl-2-oxo-pyrrolidino)-butyramide, which melts at 93°C.

The 2-(5-methyl-2-oxo-pyrrolidino)-butyric acid, as well as the other acids which may also be used in this synthesis, can be obtained by saponification of the corresponding esters, such as those mentioned in Example 2, or by the action of alkali metal 2-halo-2-Y-acetates with a metallic derivative of the desired 2-oxo-pyrrolidine. In this way, there can be obtained, for example 2-(5,5-dimethyl-2-oxo-pyrrolidino)-butyric acid (m.p. 164°C.) and (3-methyl-2-oxo-pyrrolidino)-acetic acid (m.p. 96°C.).

Example 4

2-(5-methyl-2-oxo-pyrrolidino)-propionamide

Ammonium 2-(5-methyl-2-oxo-pyrrolidino)-propionate is prepared by neutralisation of the free acid (m.p. 128—129°C.) with an excess of a methanolic solution of gaseous ammonia. The solution of the ammonia salt is then evaporated in a vacuum

and the residue is distilled under reduced pressure; b.p. 140—145°C./0.01 mm.Hg.

After recrystallisation from a mixture of ethanol and hexane, there is obtained, in a yield of 70% of theory, 2-(5-methyl-2-oxo-pyrrolidino)-propionamide; m.p. 130°C.

Ammonium 3-(5-methyl-2-oxo-pyrrolidino)-butyrate, obtained by the neutralisation with ammonia of the corresponding free acid (m.p. 106—107°C.), gives, by thermal decomposition, 2-(5-methyl-2-oxo-pyrrolidino)-butyramide which has already been mentioned in Example 3; after recrystallisation from a mixture of ethanol and hexane, it has a melting point of 93°C.

By means of the process according to Example 4, there can be prepared all of the 2-(2-oxo-pyrrolidino)-2-Y-acetamides according to the present invention in which the amide group is not substituted.

Example 5

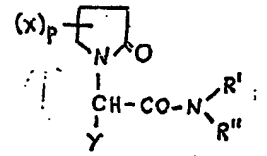
The following compounds according to the present invention are prepared by one of the processes described above:

4-(methyl-2-oxo-pyrrolidino)-acetamide; m.p. 120°C. (recrystallised from isopropanol-ether);
5-(methyl-2-oxo-pyrrolidino)-acetamide; m.p. 124°C. (recrystallised from isopropanol);
(3,3-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 130°C. (recrystallised from isopropanol);
(3,5-dimethyl-2-oxo-pyrrolidino)-acetamide (isomeric mixture); b.p. 150—155°C./0.2 mm.Hg.;
(4,5-dimethyl-2-oxo-pyrrolidino)-acetamide (isomeric mixture); m.p. 132—138°C. (recrystallised from isopropanol);
(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 149°C. (recrystallised from isopropanol);
(3,5,5-trimethyl-2-oxo-pyrrolidino)-acetamide; b.p. 150—155°C./0.05 mm.Hg.;
2-(2-oxo-pyrrolidino)-butyramide; m.p. 122°C. (recrystallised from ethanol);
2-(2-oxo-pyrrolidino)-3-methyl-butyramide; m.p. 188°C. (recrystallised from ethyl acetate);
2-(5-methyl-2-oxo-pyrrolidino)-propionamide; m.p. 130°C. (recrystallised from ethanol-hexane);
2-(5-methyl-2-oxo-pyrrolidino)-butyramide; m.p. 93°C. (recrystallised from ethanol-hexane);
(5-ethyl-2-oxo-pyrrolidino)-acetamide; b.p. 155°C./0.02 mm.Hg., m.p. 97°C. (recrystallised from ethanol-ether);
(4,5-dimethyl-2-oxo-pyrrolidino)-N,N-dimethyl-acetamide; b.p. 148—150°C./1.5 mm.Hg.;
(5,5-dimethyl-2-oxo-pyrrolidino)-N,N-diethyl-acetamide; b.p. 128—129°C./0.1 mm.Hg.;
2-(4-methyl-2-oxo-pyrrolidino)-propionamide; m.p. 106°C. (recrystallised from ethanol-hexane);
2-(4-methyl-2-oxo-pyrrolidino)-butyramide; m.p. 126°C. (recrystallised from ethanol-hexane);
2-(4,5-dimethyl-2-oxo-pyrrolidino)-propionamide; m.p. 138—139°C. (recrystallised from ethanol-hexane);
N-allyl-(3-methyl-2-oxo-pyrrolidino)-acetamide; b.p. 148°C./0.05 mm.Hg.;
N-*n*-butyl-(3-methyl-2-oxo-pyrrolidino)-acetamide; b.p. 175°C./0.01 mm.Hg.; m.p. 54°C. (recrystallised from toluene-hexane);
(3,4-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 123°C. (recrystallised from ethanol-ether);
(4,4-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 150°C. (recrystallised from ethanol);
N-*n*-propyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 77°C. (recrystallised from hexane);
N-isopropyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 100°C. (recrystallised from ether-hexane);
N-allyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 102°C. (recrystallised from ether);
N-propargyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide; m.p. 118°C. (recrystallised from ethyl acetate);
N-*n*-butyl-2-(5,5-dimethyl-2-oxo-pyrrolidino)-butyramide; b.p. 135°C./0.1 mm.Hg.;
N-[(5,5-dimethyl-2-oxo-pyrrolidino)-acetyl]-pyrrolidine; b.p. 160°C./0.1 mm.Hg.;

N-[(5,5-dimethyl-2-oxo-pyrrolidino)-acetyl]-piperidine; m.p. 68°C. (recrystallised from hexane);
N-[(5,5-dimethyl-2-oxo-pyrrolidino)-acetyl]-morpholine; m.p. 129°C. (recrystallised from ether).

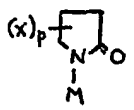
WHAT WE CLAIM IS:—

1. New N-substituted lactams of the general formula:

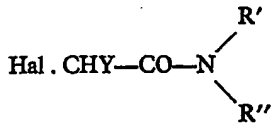


wherein X is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, p is a whole number of from 1 to 6, Y is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms or a cycloalkyl radical and R′ and R″, which may be the same or different, are hydrogen atoms or alkyl, alkenyl, alkynyl, cycloalkyl or aryl radicals or R′ and R″, together with the nitrogen atom to which they are attached, form a heterocyclic radical which may contain further heteroatoms, with the proviso that at least one of the symbols X and Y is other than a hydrogen atom.

2. (5-methyl-2-oxo-pyrrolidino)-N,N-diethylacetamide.
3. (3-methyl-2-oxo-pyrrolidino)-acetamide.
4. 2-(2-oxo-pyrrolidino)-propionamide.
5. 2-(5-methyl-2-oxo-pyrrolidino)-butyramide.
6. 2-(5-methyl-2-oxo-pyrrolidino)-propionamide.
7. (4-methyl-2-oxo-pyrrolidino)-acetamide.
8. (5-methyl-2-oxo-pyrrolidino)-acetamide.
9. (3,3-dimethyl-2-oxo-pyrrolidino)-acetamide.
10. (3,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
11. (4,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
12. (5,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
13. (3,5,5-trimethyl-2-oxo-pyrrolidino)-acetamide.
14. 2-(2-oxo-pyrrolidino)-butyramide.
15. 2-(2-oxo-pyrrolidino)-3-methyl-butyramide.
16. (5-ethyl-2-oxo-pyrrolidino)-acetamide.
17. (4,5-dimethyl-2-oxo-pyrrolidino)-N,N-dimethylacetamide.
18. (5,5-dimethyl-2-oxo-pyrrolidino)-N,N-diethylacetamide.
19. 2-(4-methyl-2-oxo-pyrrolidino)-butyramide.
20. 2-(4-methyl-2-oxo-pyrrolidino)-propionamide.
21. 2-(4,5-dimethyl-2-oxo-pyrrolidino)-propionamide.
22. N-allyl-(3-methyl-2-oxo-pyrrolidino)-acetamide.
23. N-*n*-butyl-(3-methyl-2-oxo-pyrrolidino)-acetamide.
24. (3,4-dimethyl-2-oxo-pyrrolidino)-acetamide.
25. (4,4-dimethyl-2-oxo-pyrrolidino)-acetamide.
26. N-*n*-propyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
27. N-isopropyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
28. N-allyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
29. N-propargyl-(5,5-dimethyl-2-oxo-pyrrolidino)-acetamide.
30. N-*n*-butyl-2-(5,5-dimethyl-2-oxo-pyrrolidino)-butyramide.
31. N-[(5,5-dimethyl-2-oxo-pyrrolidino)-acetyl]-pyrrolidine.
32. N-[(5,5-dimethyl-2-oxo-pyrrolidino)-acetyl]-piperidine.
33. N-[(5,5-dimethyl-2-oxo-pyrrolidino)-acetyl]-morpholine.
34. Process for the preparation of compounds of the general formula given in claim 1, wherein a 2-pyrrolidinone derivative of the general formula:—

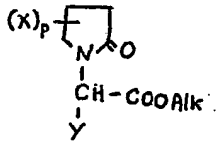


in which X and p have the same meanings as in claim 1 and M is an alkali metal atom, is reacted with a 2-haloacetamide derivative of the general formula:—



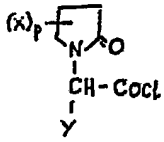
in which R′, R″ and Y have the same meanings as in claim 1 and Hal is a halogen atom.

35. Process for the preparation of compounds of the general formula given in claim 1, wherein a pyrrolidinone derivative of the general formula:—



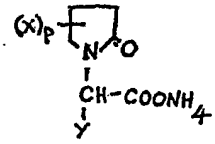
in which X, Y and p have the same meanings as in claim 1 and Alk is a lower alkyl radical, is reacted with a nitrogen compound of the general formula R′ . NH . R″, in which R′ and R″ have the same meanings as in claim 1.

36. Process for the preparation of compounds of the general formula given in claim 1, wherein an acetyl halide of the general formula:—



in which X, Y and p have the same meanings as in claim 1, is reacted with a nitrogen compound of the general formula R′ . NH . R″, in which R′ and R″ have the same meanings as in claim 1.

37. Process for the preparation of compounds of the general formula given in claim 1, in which R′ and R″ are both hydrogen atoms, wherein an ammonium acetate derivative of the general formula:—



in which X, Y and p have the same meanings as in claim 1, is subjected to thermal dehydration.

38. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

39. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 34—38.

40. Pharmaceutical compositions, comprising at least one compound of the general formula given in claim 1, in admixture with a solid or liquid pharmaceutical excipient.

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